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Module 1: History and Ethical Principles

Introduction

The first century physician Celsius justified experiments on condemned criminals in Egypt using wording that became a classic defense for hazardous experimentation: "It is not cruel to inflict on a few criminals sufferings which may benefit multitudes of innocent people through all centuries." Brady and Jonsen

This section will provide

a. a brief history of research in which the investigators did not adequately protect the rights and welfare of participants; and,
b. an introduction to the ethical principles that guide us today.

Ethical Decision Making

What is the difference between ethics and morality? Morality asks the question what should one's behavior and character be? While ethics is the disciplined study of the morality of individuals or populations.

There are two kinds of ethics: Descriptive ethics and normative ethics. Descriptive ethics asks the question, "What are the moral beliefs and practices of an individual, groups of individuals, institutions, or society?" In ethical decision making we are not very concerned with descriptive ethics.

We are, however, concerned with normative ethics, where questions such as What ought morality to be? How should researchers behave? How should researchers not behave? What character traits should researchers cultivate as virtues? And, what character traits should researchers try to avoid?

How do we come to make an ethical decision? close the new window to return here.

The advantages of understanding research ethics are

1. research ethics provides us with a structure for analysis and decision-making; and
2. research ethics helps us to make decisions in a more disciplined way.

How do ethical conflicts arise? close the new window to return here.

History of Research Ethics

Before the mid-19th century the use of human subjects in experimentation was not well disciplined and generally not subject to a rigorous scientific method. Among the first human subject research experiments to be documented were the vaccination trials in the 1700's. In these initial trials the physicians themselves or their family members were used as the test subjects. Edward Jenner first tested smallpox vaccines on his son and on neighborhood children. Johann Jorg (1779-1856) swallowed 17 drugs in various doses to record their properties. Louis Pasteur, even though he was confident of the results obtained through animal trials, "agonized over treating humans," and finally did so only when he was convinced the death of the child, the first test subject, "appeared inevitable." Rothman

In 1721, condemned prisoners in England were offered a reduced sentence if they would take part in inoculation trials Grodin . Before allowing her own children to receive a smallpox vaccine inoculation, Caroline the Princess of Wales "begged the lives" of six prisoners to first test the vaccine and later approved the use of six charity children from St. James's parish, to test the safety of the inoculation process Lasagna.

The era of modern science started in the 1900's and the progress of medicine began to accelerate. Walter Reed's well-known experiments to develop an inoculation for yellow fever were at the forefront of these advances. These experiments, however, unlike earlier experiment with vaccinations, were carefully scrutinized.

In the early decades of the 1900's, medical advancements positively impacted communities and the medical profession was highly regarded. Medical research received wide support. In 1941, President Franklin Roosevelt created the Committee on Medical Research which had the charge to coordinate medical research in the United States and around the world. Millions of dollars were spent in an effort to eradicate dysentery, influenza, venereal disease and malaria Rothman. See Dialog from testimony before the Royal Commission of Vivisection 1908. Society's high regard for the medical profession, however, was not to last. At the end of World War II, 23 Nazi doctors and scientists were put on trial for the murder of concentration camp inmates who were used as research subjects. Of the 23 professionals tried at Nuremberg, 15 were convicted, 7 were condemned to death by hanging, 8 received prison sentences from ten years to life, and 8 were acquitted Mitscherlich & Mielke . Included in the legal judgment and sentences handed down at the culmination of the trial were ten points describing required elements of conducting research with humans. These points became known as the Nuremberg Code.

Nuremberg Code

The Nuremberg Code includes the following guidance for researchers:

- Informed consent is essential
- Research should be based on prior animal work
- The risks should be justified by the anticipated results
- Only qualified scientists must conduct research

- Physical and mental suffering must be avoided
- Research in which death or disabling injury is expected should not be conducted

Effect of the Nuremberg Code

The Code had little impact on researchers in the U.S who thought the principles in the Code were already implicit in their work and that it was simply a document to condemn the Nazi atrocities and to convict the Nazi doctors. There were a number of problems with the Code itself. For example it did not have the strength of law, it was created post hoc, and it applied to only non-therapeutic human subjects research.

Declaration of Helsinki

In 1964 the World Medical Association developed a code of research ethics that came to be known as the Declaration of Helsinki. It was a reinterpretation of the Nuremberg Code, with an eye to medical research with therapeutic intent. Subsequently, journal editors required that research be performed in accordance with the Declaration. In principle, this document set the stage for the implementation of the Institutional Review Board (IRB) process. Shamoo & Irving

Beecher Article

In 1966 Dr. Henry K. Beecher, an anesthesiologist, wrote an article (Beecher HK. "Ethics and Clinical Research" NEJM June 16, 1966) describing 22 examples of research studies conducted by reputable researchers and published in major journals with controversial ethics. Beecher wrote, "medicine is sound, and most progress is soundly attained," however if unethical research is not prohibited it will "do great harm to medicine." He continues by describing estimates of the number of unethical studies and concludes, "unethical or questionably ethical procedures are not uncommon." Beecher Beecher's article played an important role in heightening the awareness researchers, the public, and the press to the problem of unethical human subjects research.

> *"Until this article we assumed that unethical research could only occur in a depraved regime like the Nazis"*- Robert J. Levine, MD (personal communication)

Increased public awareness brought to light numerous additional human subjects studies that had been conducted without appropriate regard to sound ethical principles. Several examples of such studies are presented below.

Wichita Jury Study

In 1953, with approval of lawyers on both sides, the deliberation rooms for 6 juries were bugged without the knowledge of the juries. The investigators wanted to learn more about the deliberation process and believed that if the jurors knew they were being recorded the deliberation would be constrained

and less rigorous.

Ethical problems:
jurors and those on trial. NIH

Willowbrook Hepatitis Study

In 1956, at an institution for mentally retarded children in Staten Island, New York, a study was initiated to determine the natural history of viral hepatitis and to test the effectiveness of gamma globulin as an agent for inoculating against hepatitis. The children were deliberately infected with a mild form of hepatitis. The investigators defended the study by stating that most new children would become infected with hepatitis within their first 6-12 months at the institution. Although consent was obtained from parents, the parents were not fully informed of the possible hazards involved in the study. Furthermore, there is evidence that the parents were led to believe that the child would not be enrolled at the school unless the parents signed the consent form.

Ethical problems:
information about risks, coercion or undue pressure on parents to volunteer their children. Munson

Jewish Chronic Disease Study

In 1963 live cancer cells were injected into senile patients without their knowledge as part of a study of immunity to cancer. Since the investigators believed that the cells would be rejected, the researchers did not inform the patients or seek consent because they didn't want to frighten them.

Ethical problems:
subjects. Levine

San Antonio Contraception Study

In San Antonio, Texas, a number of Mexican-American women participated in a 1971 study to determine side effects of an oral contraceptive. The women came to a clinic seeking contraceptives. Unbeknownst to them, the study was designed so that half the women would receive oral contraceptives for the first half of the study, then switched to placebo. The women initially receiving placebo were placed on the oral contraceptive for the second half of the study. 10 of the 76 participants became pregnant while using placebo.

Ethical problems:
subjects, risks to subjects outweighed benefits. Levine

Tea Room Trade Study

The organization of the study was first to obtain information about homosexual practices in public restrooms and then to conduct further

investigation on the men who took part in the acts. The researcher went undercover and gained the confidence of the men by acting as a "look out." The researcher identified 100 active participants by tracing their car license numbers. A year after he completed the initial study of direct observation of homosexual acts the researcher distributed a "social health survey" throughout the communities where he knew the participants lived.

Ethical problems: use of a vulnerable population, reinforced image that social scientists use deception casually in research, lack of informed consent. Warwick

Obedience to Authority Study (Milgram Study)

The purpose of this study was to determine response to authority in normal humans. The researchers told recruited volunteers that the purpose was to study learning and memory. Each subject was told to teach a "student" and to punish the students' errors by administering increasing levels of electric shocks. The "student" was a confederate of the researcher who pretended to be a poor learner and mimicked pain and even unconsciousness as the subject increased the levels of electric shock. 63% of the subjects administered lethal shocks; some even after the "student" claimed to have heart disease. Some of the subjects, after being "debriefed" from the study experienced serious emotional crises.

Ethical Problems: deception, unanticipated psychological harms.

The Public Health Service Syphilis Study (1932-1971)

This study is among the most influential in shaping public perceptions of research involving human subjects. Initiated by the Public Health Service, it was designed to document the natural history of syphilis in African-American men. At the time the study began there was no known treatment for syphilis. Hundreds of men with syphilis and hundreds of men without syphilis (serving as controls) were enrolled into the study. The men were recruited without truly informed consent. They were deliberately misinformed regarding the necessity for some of the procedures. For example, spinal taps were described as necessary and special "free treatment." Even after penicillin was found to be a safe and effective treatment for syphilis in the 1940's, the men were denied antibiotics. The study continued to track these men until 1972 when the first public accounts of the study appeared in the national press. The study resulted in 28 deaths, 100 cases of disability, and 19 cases of congenital syphilis. Levine

Ethical problems: lack of informed consent, deception, withholding information, putting men and their families at risk, exploitation of a vulnerable

After the press "blew the whistle" on the Syphilis Study, an Ad Hoc Panel was formed by Congress. The panel determined that the study should be stopped immediately and that oversight of human research was inadequate. The Panel recommended that federal regulations be designed and implemented to

protect human research subjects in the future. Subsequently, the following regulations were enacted:

- National Research Act
- May 1974 - 45 CFR 46
- 1981 - 45 CFR 46 revised
- 1981 - 21 CFR 50

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The Belmont Principles

In 1974 Congress authorized the formation of the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research, known to most people in research ethics as The National Commission. Congress charged the National Commission to identify the basic ethical principles that underlie the conduct of human research. They asked the National Commission to look at the writings and discussion that had taken place up to this time and to ask, "What are the basic ethical principles that people are using to judge the ethics of human subject research?" Congress also asked the National Commission to develop guidelines to assure that human research is conducted in accordance with those principles. The National Commission met and in 1979 published the *Belmont Report*. The *Belmont Report* is "must reading" for everyone involved in human subject research.

The *Belmont Report*
human subject research. These principles are commonly called the Belmont Principles. The Belmont Principles are respect for persons, beneficence, and justice.

Respect for Persons:
for persons. It reminds us that we must treat individuals as autonomous human beings and not use people as a means to an end. We must allow people to choose for themselves, and provide extra protection to those with limited autonomy.

The derived rules include:

- The requirement to obtain informed consent
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- What are the elements of autonomy? **Click here to see** . Close the new window to return here
- Autonomy is covered in more detail in Module 7, Vulnerable Subjects: A Definition

Beneficence: This principle refers to acts of kindness or charity that go beyond duty. It reminds us to minimize harms and maximize benefits. The derived rules include:

- The requirement to use the best possible research design to maximize benefits and minimize harms
- The requirement to make sure the researchers are able to perform the procedures and handle the risks
- The requirement to prohibit research that is without a favorable risk-benefit analysis.

Justice: The principle of justice reminds us to treat people fairly and to design research so that its burdens and benefits are shared equitably. The derived rules include:

- The requirement to select subjects equitably
- The requirement to avoid exploitation of vulnerable populations or populations of convenience

It was the Commission's intention that each of the three principles should have equal moral force. This means that in some situations, the 3 principles might be in conflict with one another. For example, we might derive from the principle of respect for persons that we should limit the involvement of children in research because children are unable to choose for themselves. But, we would derive from the principle of justice that the involvement of children in research is necessary because only by involving children in research will children have the opportunity to benefit from the research. The *Belmont Report*
outweighs another, rather, we are required to consider each case separately and on it's own merits to determine what the appropriate ethical decision should be.

Key Issues in Research Ethics

Definition of "Risk"

Risks are generally evaluated according to the probability that they will occur. Is the risk something that will occur in almost all subjects or in only one of 10,000 subjects? We can also quantify risk according to the magnitude of harm. Will the harm consist of some minor itchiness, or will the potential harm be death? Risks can also be classified according to their type. In medical research we often focus on physical risk. However, risks may also be social, legal, economic or psychological in nature. In addition, risks may apply to the individual subject or may apply to a broader segment of the society.

Definition of "Benefit"

A benefit is defined as the value or advantage of being part of the research study. This value or advantage might be a greater chance of having a good therapeutic outcome. Alternatively it might be more intangible. For example the results from a study could provide crucial information to understand the

underlying socioeconomic causes of drug addiction. This then presents the problem of weighing potential risks to the subject or society with the potential benefits.

When a risk benefit analysis is conducted, the probability of harm relative to the probability of benefit is determined. As an aside, payment for study participation should never be considered a benefit and it is not ethically sound to rebalance the risk benefit ratio by providing financial compensation to study participants.

PI's Relationship with Staff

A responsible PI will:

- Obtain team management skills (CRM) Close the new window to return here.
- Encourage questions from colleagues and staff.
- Listen to the concerns of the research staff, they may be the first to point out problems with the protocol and with compliance.
- Build consensus with the research team.
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Authority relationships are not limited to the principal investigator and the staff, but, can also include the authority of the sponsor over the principal investigator, the authority of the principal investigator over the subject and the

Investigator-Subject Relationship

The investigator must place the subject's rights, welfare and safety above all other personal and scientific concerns. The relationship between researcher and subject is similar to a physician-patient relationship, but different in the following ways:

- **Informed consent is required in the Investigator-Subject relationship**

  EXAMPLE: Hypothetically let's say that a patient should provide consent for a procedure, but the patient insists that she does not want to hear about the risks, benefits alternatives, and further insists that the physician decide for her. Many would say that it is ethical for the physician to go ahead with the treatment, provided that he/she is

  In research the issue is more complex and the relationship more formal. If a potential research subject is given a consent form and the subject does not want to read the document and simply asks, "Where do I sign," the investigator must ethically insist that the subject listen to the investigator's description of the study and other important information. Further the Investigator must insist that the potential subject read and understand the consent document. If the subject refuses to read the consent or hear a full disclosure of the information about the research,

then the investigator has the ethical obligation to prohibit enrollment of the subject.

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EXAMPLE: It is common in basic science laboratories to obtain blood from normal volunteers, usually staff in the research lab. Some blood donors have bad veins and may need to be stuck several times to obtain blood. This could present a problem to the potential subject. Since they are staff in the PI's lab, they might however, say, "Stick me. I don't care. I don't mind needles." Responsible investigators should recognize the problem and excuse such a person from the study. The investigator should say something to the effect, "You are experiencing more harm than the average subject. I will find someone else to enter the study who who will not experience the same anxiety and harm."

- **The investigator has a moral fiduciary relationship with the subject**

EXAMPLE: There are conflicts of interest that are so great that even the moral investigator will have a difficult time making the right decision. If doing what is right for the subject means that you will lose $10 million, many of us could be susceptible to making the wrong decision. It is up to the IRB to detect and minimize these conflicts of interests. However, it is also up to the investigator to avoid entering into these untenable conflicts.

Recent Research Concerns

Most readers realize the last several years of discovery involving unethical studies including gene therapy, cancer, and psychiatric research has heightened the public awareness of these issues even further. Some recent examples follow:

- **Death of Normal Volunteer** On March 31, 1996, a 19-year-old Asian American student at the University of Rochester responded to an advertisement for study subjects to undergo bronchoscopy for the harvest of alveolar macrophages. The bronchoscopy was difficult and required numerous doses of topical lidocaine. The investigators repeatedly asked subject if she wanted to continue and the subject nodded her head yes. The study was completed, but the subject returned to the hospital cardiac arrest from an overdose of lidocaine and died April 2, 1996. An investigation into this death revealed that the protocol did not limit lidocaine dose, that the doses were not documented, that the subject was not observed after the bronchoscopy, and that the concentrations of lidocaine were increased without IRB approval.

- **Death on Gene Therapy Trial** In the fall of 1999, eighteen year old Jesse Gelsinger died as a result of his participation in a gene therapy trial. Jesse had a rare metabolic disorder, ornithine transcarbamylase deficiency syndrome, OTC, which was being controlled by medication

and diet. Researchers were testing an innovative technique using adenovirus gene therapy. Shortly after treatment Jesse Gelsinger experienced multiple organ failure and subsequently died. This case catapulted research with human subjects into the national media. Serious concerns related to conflict of interest, data safety monitoring,

contemporary illustration of continued doubts about the ethical integrity of research with human subjects. This case has instigated deliberations on all these controversial topics at the national level. The outcome of such discussions have yet to be determined.

Ethical Problems: **informed consent, conflict of interest, data safety monitoring**

As the technologic age takes us into unknown realms of medicine, we will need to continue to review, debate, and justify research. Close examination of research with human subjects is destined to continue.

Applying Research Ethics

The Federal regulations give us the three basic protections of human subjects involved in research:

1. Review by an Institutional Review Board
2. Informed consent
3. Institutional assurances

Institutional assurances are a mechanism to apply the federal regulations to all human subject research. When institutions sign federal assurances, they may also elect to apply the Health and Human Services regulations and terms of the assurance to all research of the institution, regardless of the source of funding.

What are the criteria to decide whether or not research is ethical?

From the principle of respect for persons we need to conduct initial and continuing informed consent. We need to evaluate whether the research allows subjects to withdraw from the research and maintains the welfare of each subject.

From the principle of beneficence we need to evaluate the social and scientific value of the research, the scientific validity of the research, and determine whether the research has a favorable risk benefit ratio.

From the principle of justice we need to evaluate whether there is fair subject selection. We also need to evaluate the inclusion and exclusion criteria and the methods of recruitment.

The glue that holds this evaluation process together is the independent review by the IRB. The IRB will ask the following questions relevant to the ethical principles described in the Belmont Report:

Respect for Persons

- Does the consent process maximize autonomy?
- Does the protocol maximize autonomy?
- What additional protections have been put in place for vulnerable populations?
- Does this study maximally protect subject privacy?

Beneficence

- Is the research design adequate? Can it be improved?
- What are the risks? Have they been minimized?
- What are the benefits? Have they been maximized?

Justice

- Does recruitment for the study target the population that will benefit from the research?
- Does the recruitment unfairly target a population?
- Are the inclusion/exclusion criteria fair?

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